



A DOSE OF YOUR OWN MEDICINE? DRUG TESTING ON CHILDREN AND LABELING DRUGS FOR PEDIATRIC USE--ESSENTIAL NEEDS

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A DOSE OF YOUR OWN MEDICINE?
DRUG TESTING ON CHILDREN AND LABELING DRUGS FOR
PEDIATRIC USE—ESSENTIAL NEEDS

I. INTRODUCTION

On December 13, 1994, David Kessler, the Commissioner of the Food and Drug Administration (FDA), spoke at the Food and Drug Law Institute's 38th Annual Education Conference and declared an "FDA initiative to obtain more pediatric data throughout the drug development period and in labeling."¹ The Commissioner was speaking of the urgent need for more drug testing on children to determine appropriate pediatric use and the urgent need for an increase in the overall proportion of prescription drugs that bear labels indicating pediatric use.

Unfortunately, all children get sick. These illnesses may include anything from the common cold, strep throat, and the flu to asthma, diabetes, cancer, and AIDS. Some children will require anesthesia, emergency medical drugs, or neurological drugs. Children may need commonly prescribed drugs or they may need experimental drugs. Regardless of these facts, more than 75% of the drugs on the market in our country today have not been tested for either safety or effectiveness in fetuses, infants, or children.² In addition, only five of the eighty drugs hospitals use most frequently to treat infants and newborns

¹David A. Kessler, *Remarks by the Commissioner of Food and Drugs*, 50 FOOD & DRUG L. J. 327, 330 (1995).

²See Victor Ostrowidski, *Infants, Kids, and Drugs*, AM. DRUGGIST, May 1994, at 16, 16.

are actually labeled for pediatric use.³ Doctors are still able to prescribe these drugs for children because once a drug is approved by the FDA, medical professionals can legally prescribe the drug for unapproved, off-label uses.⁴ As deputy director of the FDA's Office of Drug Evaluation I, Paula Botstein, indicated, "physician labeling [usually] includes a disclaimer that says safety and effectiveness have not been established for use in children."⁵

This is a problem that requires immediate attention. Children are not just miniature adults; a child metabolizes and absorbs drugs differently than adults, making drug testing and labeling regarding pediatric use essential.⁶ This paper first addresses these needs in more detail. The histories of drug testing on children and labeling drugs for pediatric use are next addressed. Then this paper considers the current conditions of, and regulations on, drug testing and pediatric labeling. Finally, an analysis of what needs to be done to make drugs more safe and effective for use in children is given.

II. THE HEALTH AND SAFETY OF CHILDREN REQUIRE MORE DRUG TESTING ON CHILDREN AND MORE DRUGS LABELED FOR PEDIATRIC USE

³This refers to drug labels bearing information such as the dosages, indications, and contraindications for use in children. *See id.*

⁴*See* 21 C.F.R. § 312.2(d) (1996).

⁵*Why FDA is Encouraging Drug Testing in Children* (last modified Jan. 1995) <<http://fdabbs.fda.gov/fdac/special/newdrug/kidmed.html>> [hereinafter *Drug Testing in Children*].

⁶*See id.*

Growth, differentiation, and maturation make children different from adults. Childhood brings about dramatic changes in body proportions, composition, and physiology; differentiation, growth and maturation of major organ systems; rapid increases in length, weight and surface area; and changes in the proportion of body weight made up by fat, protein, and water.⁷ Changes in both metabolism and excretion throughout childhood,⁸ require drug testing on children to determine appropriate dosages; this information should then appear on drug labels so that physicians can prescribe drugs for children appropriately.

While having this information seems logical, these vital facts are generally unknown. The FDA is finally facing complaints that health care professionals are “giving ‘guesstimate’ dosages of drugs to babies and children because little or no research has been done on the proper dosages.”⁹ In 1990 the American Academy of Pediatrics estimated that 80% of drugs approved for adults, contained no information pertaining to pediatric use.¹⁰ The result is that children are dying either because doctors will not prescribe the drugs that they need or because the drugs are administered improperly.¹¹ A. *Drug Testing and Children: A Desperate Need*

“[I]t’s important to figure out what doses work best in kids and what

⁷See Ralph E. Kauffman, *Scientific Issues in Biomedical Research with Children*, in CHILDREN AS RESEARCH SUBJECTS 29, 29 (Michael A. Grodin & Leonard H. Glantz eds., 1994).

⁸See *id.*

⁹Robin E. Margolis, *Regulatory Update*, 12 No. 1 HEALTHSPAN 24, 25 (1995).

¹⁰See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 FED. REG. 64240, 64240 (1994); *Rule Would Help Doctors Prescribe Drugs for Children*, THE DES MOINES REG., Dec. 13, 1994, at 6 [hereinafter *Rule Would Help Doctors*].

¹¹See *Rule Would Help Doctors Prescribe Drugs for Children*, *supra* note 10, at 6.

kinds of adverse reactions are likely to occur,”¹² says Paula Botstein, deputy director of FDA’s Office of Drug Evaluation I, when asked why the FDA is encouraging drug testing in children. While there are advances in medicine every day, children are typically left out because pediatricians do not know how to properly prescribe these new medications since there has been no prior testing on children.¹³ This is the case with both FDA approved drugs, such as many antibiotics and anesthetics, as well as many experimental drugs used for diseases such as cancer and AIDS.

The problem is that “children are not little adults, when it comes to calculating doses or anticipating side effects,”¹⁴ said Dr. Edwin Forman, professor of pediatrics at Brown and director of the children’s cancer center at Rhode Island Hospital.

Young children metabolize, absorb, and excrete drugs at different rates than adults.¹⁵ These rates are key to determining the proper doses and dosing intervals for children.¹⁶ In addition, the processes of growth and development affect the potential for a medication to be toxic to a child.¹⁷

There are many examples showing how these biological differences lead children and adults to react differently to the same drugs. For example, some barbiturates make children hyperactive, but make adults feel sluggish.¹⁸ Am-

¹²*Drug Testing in Children*, *supra* note 5.

¹³See Irene Wielawski, *Drug Advances Leave Children out in the Cold; Few New Medicines are Being Tested on Youngsters*, L.A. TIMES, Jan. 9, 1990, at E1.

¹⁴*Id.*

¹⁵See *Drug Testing In Children*, *supra* note 5; Kauffman, *supra* note 7, at 38.

¹⁶See Kauffman, *supra* note 7, at 38.

¹⁷See *id.* at 39.

¹⁸Rebecca D. Williams, *How to Give Medicine to Children* (last modified Dec. 1996) <[http:// www.fda.gov/fdac/features.196_kid.html](http://www.fda.gov/fdac/features.196_kid.html)>.

phetamines stimulate adults, but can make children more calm.¹⁹ Aspirin, while an over-the-counter drug, clearly exemplifies this point as it can lead to Reye's Syndrome in children with chickenpox or flu symptoms, but this does not happen in adults.²⁰

Despite all of these known differences, the current level of drug testing in children is not sufficient. One reason that children are not used in clinical trials relates to the ethics involved in drug testing on children. Obtaining consent is an integral component to using children in clinical trials. Young children are not capable of providing their own consent and so it is typically left to parents.²¹ Another ethical concern is giving a sick child a placebo instead of a drug that could be a potential cure.²² Lastly, it is morally troubling, as well as difficult, to find healthy child subjects to use in clinical trials. Thus, typically children that are used for drug testing have the disease.²³

There are other roadblocks in the area of pediatric drug testing. First of all, the Federal Food, Drug, and Cosmetics Act does not authorize the FDA to require testing on children prior to approving a drug for the market.²⁴ If Congress amended the statute, the result would probably be an increase in the current average of seven to ten years it already takes for the FDA to approve New Drug Applications (NDAs).²⁵ In addition, the financial costs of such a

¹⁹ See *id.*

²⁰ See *id.*

²¹ See Leonard H. Glantz, *The Law of Human Experimentation with Children*, in CHILDREN AS RESEARCH SUBJECTS, *supra* note 7, at 103, 104. See discussion *infra* Part IV(A)(3).

²² See Ken Flieger, *Testing Drugs in People* (last modified Jan. 1995) <<http://fdabbs.fda.gov/special/newdrug/testing.html>>.

²³ See *id.*

²⁴ See 21 U.S.C. § 301–395 (1996); Wielawski, *supra* note 13.

²⁵ See Wielawski, *supra* note 13, at E1.

requirement could stifle innovation, as drug companies shirked the expense of drug testing on children by not developing new and better drugs. Finally, another reason for the limited quantity of drug testing in children is that seriously ill children constitute a very small proportion of the market, leaving pharmaceutical companies without the financial incentives to test the drugs on children.²⁶

For example, only 1.5% of those afflicted with HIV are children,²⁷ which helps to explain why the new class of AIDS drugs, protease inhibitors, have only been tested and licensed for use in adults.²⁸ A Milwaukee pediatrics AIDS physician has prescribed the drug for two children, but severely criticized the pharmaceutical industry saying that he has no information about the proper dosage or the side effects in children. He says that this is because there is no economic incentive for testing the drug on children since most AIDS patients are adults.²⁹ This is not a problem limited to protease inhibitors. Only three of the nine AIDS drugs currently available have been approved for children.³⁰ In addition, other drugs primarily used by adults such as high blood pressure medication, ulcer medication,³¹ and inhaled asthma drugs,³² have not been tested on children.

Children deserve as much of a chance to live as adults. The immorality

²⁶See *id.*; *Drug Testing in Children*, *supra* note 5.

²⁷See Debra Gordon, Leaving the Children Behind; HIV Treatment: For Adults Only?, THE VIRGINIAN PILOT, Nov. 29, 1996, at A1.

²⁸See Marilyn Marchione, *Two Area Children Being Treated Experimentally with New Class of AIDS Drugs*, MILWAUKEE J. SENTINEL, Nov. 30, 1996, at 3.

²⁹See *id.*

³⁰See Gordon, *supra* note 27, at A1; *Pharmacia & Upjohn Rescriptor not Recommended for Use with Protease Inhibitors*, FDA Committee Says, 58 F-D-C REP. ("The Pink Sheet"), Dec. 2, 1996, at 18.

³¹See Elizabeth Stone, *Kids' Dosages Debated*, CHICAGO TRIBUNE CO., Jan. 31, 1995, at 7.

³²See Wielawski, *supra* note 13, at E1.

in this situation lies with the pharmaceutical company that does not test drugs on children because it is not cost-effective. The problem here is clear; there is an urgent need for an increase in drug testing on children.

B. Pediatric Use Labeling: Another Desperate Need

If a drug is not tested on children then the drug label will almost always bear nothing relevant to usage in children.³³ Since so few drugs are tested for safety and effectiveness in children, it is appalling, but not shocking, that 75-80% of all drugs have no pediatric information on the label.³⁴

While there is little testing and little information on labels, health professionals can still prescribe a drug for a child as an off-label use. Thus, over time, these medical experts can gain experience with a drug and determine what dosage is appropriate for a child. Anesthesia drugs, which are often prescribed for children, but are not specifically approved or labeled for children, are a good example of how professionals learn through trial and error what the proper dosages are.³⁵ This informal testing of drugs on children is integral to calibrating appropriate dosages. Once physicians have figured these levels out (albeit not in the most favorable manner), this information should be on the drug label so that other physicians need not go through the trial and error process.

Cancer drugs for children provide a clear example of the need for pediatric use labeling. Dr. Edwin Forman, director of the children's cancer center at Rhode Island Hospital explained that cancer drugs are very toxic and can therefore have very serious side effects, especially when improper dosages are

³³The 1994 regulation, which will be discussed in detail later in this paper, is aimed at changing this. Currently, almost all drugs used by children still do not have labels indicating pediatric usage.

³⁴See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 FED. REG. 64240, 64240 (1994).

³⁵See *Drug Testing in Children*, *supra* note 5; *Rule Would Help Doctors Prescribe Drugs for Children*, *supra* note 10.

given. These drugs, he says, are marketed for adults before they are tested on children. Dr. Forman is part of the Pediatric Oncology Group, an organization which maintains a data bank regarding the use of these drugs on children so that the pediatricians can share their experiences with the drugs.³⁶ Unfortunately, there are not enough networks like this to replace the need for pediatric use to appear on the labels.³⁷

On December 13, 1994, the FDA promulgated a final rule revising pediatric use labeling.³⁸ The pharmaceutical companies have extended the compliance deadline of this rule until April 7, 1997,³⁹ but it hopefully will increase the amount of drugs bearing pediatric labeling. The FDA's justification for this rule effectively conveys the need for pediatric use labeling:

FDA continues to be concerned that, without adequate information, practitioners may be reluctant to prescribe certain drugs for their pediatric patients, or may prescribe them inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.⁴⁰

III. A HISTORICAL ANALYSIS

³⁶ See Wielawski, *supra* note 13, at E1.

³⁷ See *id.*

³⁸ See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 FED. REG. at 64240.

³⁹ See Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling; Extension of Compliance Date, 61 FED. REG. 68623, 68623 (1996).

⁴⁰ Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling, 59 FED. REG. at 64240.

A. *The History of Drug Testing on Children*

Societal treatment of children has varied immensely and the history of drug testing on children reflects the trends. In essence, as society became more concerned with child welfare, the use of children in drug testing became more obsolete. It is only somewhat recent that using children in clinical trials has been viewed as a practice that could be consonant with child welfare.

Very early history reflects the “relative social invisibility of children” as they were virtually excluded from medical discussions.⁴¹ Although the Hippocratic texts from the third century BC had some discussion of childhood diseases and suggested that children were not just little adults, there was no systematic discussion of pediatric care.⁴² The first English, pediatric medical text was probably Thomas Phaïre’s 1545, *Book of Children*.⁴³

The eighteenth century was a period marked by the indenturing of children, who became seen as valuable economic commodities.⁴⁴ In terms of medical experimentation, adults were using children (and slaves) as their research subjects.⁴⁵ For example, in response to the smallpox epidemic in England, Zadiel Boylston attempted variolation on his two sons and his two slaves.⁴⁶ Soon vaccination, inoculating people with small amounts of the disease, became popular. Jenner vaccinated his one-year old son with smallpox.⁴⁷ Physician, Benjamin

⁴¹Susan E. Lederer & Michael A. Grodin, *Historical Overview: Pediatric Experimentation in CHILDREN AS RESEARCH SUBJECTS*, *supra* note 7, at 3, 4.

⁴²*See id.*

⁴³*See id.*

⁴⁴*See* Tim Hacsí, *From Indenture to Family Foster Care: A Brief History of Child Placing in HISTORY OF CHILD WELFARE* 155, 156 (Eve P. Smith et al. eds., 1996).

⁴⁵*See* Lederer & Grodin, *supra* note 41, at 4.

⁴⁶*See id.*

⁴⁷*See id.* at 5.

Waterhouse, vaccinated eight of his children with smallpox and then tested the effectiveness by exposing three of them to people afflicted with smallpox.⁴⁸ In 1801, Nathaniel Chamman inoculated children from the Philadelphia Almshouse with measles.⁴⁹

The Industrial Revolution made children even more economically valuable and therefore protected. It was at this time that childhood was seen as a distinct phase of development. Only poor children were indentured.⁵⁰ In the 1850s, the first children's hospitals opened in New York and Philadelphia and in 1888 the American Pediatric Society was first established.⁵¹ The Society for the Prevention of Cruelty to Children (SPCC) was formed in the 1870s; many children thought to be abused or neglected were then placed in orphan asylums or institutions.⁵² The poor social conditions of the late nineteenth century left many of these institutions ripe for epidemics; pediatricians tried to help these children.⁵³ Alfred Hess, medical director of the Hebrew Infant Asylum in New York City, began experimenting on the institutionalized children and Walter Reed and George Miller Sternberg studied smallpox on the children in Brooklyn orphanages.⁵⁴ In 1885, Louis Pasteur administered the first rabies vaccine to a nine year old boy who had been bitten fourteen times by a rabid dog.⁵⁵

Remember, however, the late nineteenth century was also a period

⁴⁸ *See id.*

⁴⁹ *See id.*

⁵⁰ *See id.* at 6.; Hacsí, *supra* note 44 at 158. Indenturing was sending children to live with other families to work on their property and learn a trade.

⁵¹ *See Lederer & Grodin, supra* note 41, at 6.

⁵² *See Hacsí, supra* note 44, at 163.

⁵³ *See Lederer & Grodin, supra* note 41, at 6.

⁵⁴ *See id.* at 6-7.

⁵⁵ *See id.* at 7.

when children came to be valued as demonstrated by the formation of the Society for the Prevention of Cruelty to Children and the American Pediatric Society. Attempts were made to seek out and rescue children from abuse and poverty.⁵⁶ Thus, there was also criticism of the use of children for experimentation. For example, Arthur Howard Wentworth performed spinal taps on twenty-nine children and then released a report saying that this process was momentarily painful, but essentially harmless.⁵⁷ The publication of his study produced enormous backlash.⁵⁸

By the early twentieth century, as a result of the Wentworth study, state legislators were considering bills which would have prohibited experimentation on children, but none were enacted.⁵⁹ Alfred Hess, of the Hebrew Orphan Asylum, was also criticized for using “orphans as guinea pigs.”⁶⁰ After several children died from the distribution of tetanus-infected diphtheria antitoxin, Congress passed the Biologics Act of 1902, which required the licensing of biological drugs sold in interstate commerce.⁶¹

There was, however, almost no federal policing of the treatment of children during much of the first half of the twentieth century. Thus, in the drug experimentation arena, there were no guidelines for the use of human subjects. The scientific community and bad publicity did serve as the impetus for some scientists to obtain parental consent prior to drug testing on children.⁶²

⁵⁶ See Hacsí, *supra* note 44 at, 163.

⁵⁷ See *id.* at 11.

⁵⁸ See *id.* at 12.

⁵⁹ See *id.*

⁶⁰ *Id.* at 13.

⁶¹ See Thomas A. Hayes, *Drug Labeling and Promotion: Evolution and Application of Regulatory Policy*, 51 FOOD AND DRUG L.J. 57, 59 (1996).

⁶² See *id.* at 14.

In 1935, scientists, such as John Kolmer and Maurice Brodie, tested their polio vaccines on themselves, their own children, and then small groups of children whose parents had volunteered them before they tested them on large numbers of children.⁶³ 1935 was also the year for enactment of Title IV of the Social Security Act, Aid to Dependent Children.⁶⁴ This Act increased the funds available for poor families so that many of the families that would have turned to orphan asylums or child-placing agencies were able to keep their children.⁶⁵ These changes led to a trend towards preventing child abuse and neglect, rather than rescuing children from poverty.⁶⁶ Amidst this political and social background, Kolmer and Brodie were soon denounced as murderers for the many deaths they caused with their experimental polio vaccines.⁶⁷

World War II brought about more governmental involvement in protecting children. Foster care became a popular alternative to institutions so that children could be raised in familial settings.⁶⁸ The Committee for Medical Research (CMR) assessed applications to perform medical research on children in orphanages.⁶⁹ Government interest in medical research grew tremendously after the War as appropriations for the National Institute of Health (NIH) grew from \$700,000 in 1946 to over \$55 million in 1955.⁷⁰ In addition, after World War II, the world was appalled by the experiments performed on those

⁶³ See *id.* at 15.

⁶⁴ See Hacsí, *supra* note 44, at 167.

⁶⁵ See *id.*

⁶⁶ See Roger J.R. Levesque, *The Failures of Foster Care Reform: Revolutionizing the Most Radical Blueprint*, 6 MD. CONTEMP. LEGAL ISSUES 1, 5 (1994-1995).

⁶⁷ See Lederer & Grodin, *supra* note 44, at 15.

⁶⁸ See Hacsí, *supra* note 44 at 167.

⁶⁹ See Lederer & Grodin, *supra* note 44, at 15.

⁷⁰ See *id.* at 16.

in concentration camps. The Nuremberg Code was issued in 1948, delineating standards for medical ethics.⁷¹

While there still were no federal child abuse or human research subject statutes on the books, the 1960s were a time for concern about welfare. In 1962, the article, *Battered Child Syndrome* was published⁷² and in 1966 Henry Beecher published an ethical critique of clinical experimentation in the *New England Journal of Medicine*.⁷³ In 1962 the Kefauver-Harris Amendments to the Food, Drug, and Cosmetics Act mandated informed consent of all human subjects.⁷⁴ The FDA strengthened this policy in 1967 by requiring the consent to be in writing.⁷⁵

From 1950-1970 there were studies of the hepatitis virus at the Willowbrook State School, an institution for severely mentally retarded children.⁷⁶ As opposed to the vaccine trials, these hepatitis trials involved the intentional infection of the children with the hepatitis virus.⁷⁷ While there was parental consent for the trials, Henry Beecher again criticized the experimentation saying that parents were not adequately informed of the risks, that it was problematic for children to participate when there were no anticipated therapeutic benefits, and that it was unethical for parental consent to be used as an admissions criterion to the overly crowded institution.⁷⁸

⁷¹See Richard C. Thompson, *Protecting Human Guinea Pigs* (last modified Jan. 1995) <<http://fdabbs.fda.gov/fdac/special/newdrug/guinea.html>>.

⁷²See Hacsí, *supra* note 44, at 168.

⁷³See Lederer & Grodin, *supra* note 41, at 16.

⁷⁴Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. § 355(I)(3)). See also Thompson, *supra* note 71.

⁷⁵See *id.*

⁷⁶See Lederer & Grodin, *supra* note 41, at 17.

⁷⁷See *id.* at 18.

⁷⁸See *id.*

The seventies became a time for regulation. In 1974, the Child Abuse Prevention and Treatment Act ⁷⁹ was enacted as a federal attempt to recognize and eliminate the devastating problem of child abuse. Similarly, the federal government acknowledged its need to protect research subjects.

On October 9, 1973 a notice of proposed rule-making was published in the Federal Register suggesting regulations that would require committee approval for any research supported by a Department of Health, Education and Welfare grant or contract which involved risk to human subjects.⁸⁰ In November 1973, a draft document regarding the protection of human subjects was published in the Federal Register, which regarded, “[i]nformed consent [as] the keystone of the protection of human subjects involved in research, development, and demonstration activities.”⁸¹ Children, prisoners, and the mentally infirm were identified as people having limited capacities to make informed choices. It proposed additional regulations for these vulnerable populations.⁸² On May 30, 1974, final guidelines for the protection of human subjects were published in the Federal Register, but they made no explicit reference to the protection of children.⁸³ As the proposal indicated, this rule ensured that any activity supported by a Department of Health, Education, and Welfare grant or contract involving human subjects would be reviewed and approved to determine whether the benefits outweighed the risks, whether the rights and welfare of

⁷⁹Pub. L. No. 93-247, 88 Stat. 4 (1974).

⁸⁰See Protection of Human Subjects, 38 FED. REG. 27882, 27882 (1973).

⁸¹Protection of Human Subjects, 38 FED. REG. 31738, 31738 (1973).

⁸²See *id.*

⁸³See Protection of Human Subjects, 39 FED. REG. 18914, 18914 (1974) (to be codified at 45 C.F.R. § 46); See also Lederer & Grodin, *supra* note 44, at 19.

the subjects would be protected, and whether there would be legally effective informed consent.⁸⁴

On July 12, 1974, Congress passed the National Research Act.⁸⁵ Title two of the Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Commission) to study and identify ethical principles for research on human subjects and then make recommendations for appropriate guidelines.⁸⁶ The Commission was also supposed to propose requirements regarding informed consent of children, prisoners, and the mentally infirm.⁸⁷

In 1976, the FDA promulgated regulations requiring Institutional Review Boards (IRBs) to examine all studies using institutionalized subjects.⁸⁸ After being advised by the Commission, in 1981 this regulation was amended to require IRB review for all studies of FDA-regulated products before they could be tested on humans.⁸⁹

The Commission also developed a Report and Recommendations regarding research involving children, which was published in the Federal Register on January 13, 1978.⁹⁰ The report stated that

research involving children is important for the health and well being of children but... such research [should] be conducted only if it is scientifically sound, will contribute significantly to generalizable

⁸⁴See Protection of Human Subjects, 45 C.F.R. § 46.2 (1974).

⁸⁵Pub. L. No. 93-348, 88 Stat. 342 (1974).

⁸⁶See *id.* See also Lederer & Grodin, *supra* note 44, at 19.

⁸⁷See Pub. L. No. 93-348, 88 Stat. 342 (1974).

⁸⁸See Thompson, *supra* note 71.

⁸⁹See *id.* at 2.

⁹⁰See Protection of Human Subjects: Research Involving Children; Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 43 FED. REG. 2084 (1978).

knowledge, risks are minimized, and the research performed in connection with necessary treatment wherever possible. Adequate provisions must be made to obtain the assent of the child and the consent of the parents or guardians.⁹¹

The Commission recognized the tension between the need for research on children and the vulnerability of children.⁹² The Commission felt that children should be involved in research because adult and animal models would not be sufficient for conducting research since some diseases are limited to children and since children are not merely small adults.⁹³ The Commission, however, recognized the need for Review Board safeguards.⁹⁴ A rule with these safeguards was proposed on July 21, 1978.⁹⁵ The final rule was promulgated on March 8, 1983.⁹⁶ It implemented additional responsibilities for Institutional Review Boards when children were subjects in the research.⁹⁷ This rule essentially remains in effect today.⁹⁸

The early eighties was a time when Congress enacted statutes attempting to help children. In response to the large increase in the number of children in foster care, the Adoption Assistance and Child Welfare Act of 1980⁹⁹ was enacted to provide government funds for preventive services so that families could remain intact. The Act required states to make reasonable efforts to keep

⁹¹ *Id.*

⁹² *See id.* at 2085.

⁹³ *See id.* at 2088.

⁹⁴ *See id.* at 2085.

⁹⁵ *See* Protection of Human Subjects; Proposed Regulations on Research Involving Children, 43 FED. REG. 31786 (1978).

⁹⁶ *See* Additional Protection for Children Involved as Subjects in Research, 48 FED. REG. 9814 (1983) (codified at 45 C.F.R. § 46.401–409).

⁹⁷ *See id.*

⁹⁸ *See* 45 C.F.R. 46.401–409 (1996). *See* discussion *infra* Part IV(A)(2).

⁹⁹ Pub. L. No. 96-272, 94 Stat 501 (1980).

children with their families by saying that children could only be removed after reasonable efforts to reunify and by saying that for states to be eligible for federal reimbursement, they had to provide preventive and reunification services.¹⁰⁰ By the late 1980s, the federal government saw that this system failed to live up to its expectations because the Act attempting to encourage permanency planning led to an eagerness to place children in foster care instead of providing them with the “prevention of placement services” they needed.¹⁰¹ Thus, with more money available for foster care, many more children had been placed outside of their homes and did not have permanent families. The 1983 Regulation, Additional Protections for Children Involved as Subjects in Research, may have also had unintended consequences for children; now children are not used enough as subjects in research, leaving holes in the scientific data regarding the safety and effectiveness of drugs for children.

B. The History of Labeling Drugs for Pediatric Use

The history of labeling drugs parallels the history of the Food and Drug Administration. As the FDA gained authority and discretion to regulate food, drugs, devices, and cosmetics, it increased its regulatory hold over drug labeling. Finally, in 1994 the FDA had expanded this scope to include labeling of pediatric use.

It was not until the late nineteenth century that federal jurisdiction was seen as encompassing regulation of the safety and effectiveness of food and drugs.¹⁰² Concerns about safety after the tetanus-infected diphtheria antitoxin

¹⁰⁰ *See id.*

¹⁰¹ Levesque, *supra* note 66, at 19.

¹⁰² *See* Mr. Peter Hutt, Lecture in “Food and Drug Law” at Harvard Law School Winter

killed children¹⁰³ led to The Biologics Act of 1902,¹⁰⁴ which required licensing for biological products sold in interstate commerce. It was not until industry concern over the prevention of adulteration so that competitors could have fair playing fields that Congress enacted the 1906 Federal Food and Drugs Act.¹⁰⁵ This statute, however, gave the FDA very limited power; essentially the FDA was given enforcement power to police adulterated and misbranded products.¹⁰⁶ As far as drug labels, the Act said that a drug was misbranded if its label contained false statements about its ingredients.¹⁰⁷

Soon after the New Deal and the deaths of almost one hundred people taking the untested sulfanilamide elixir, came the passage of the 1938 Federal Food, Drug, and Cosmetics Act (FDCA).¹⁰⁸ Now the FDA had the authority to regulate the safety and effectiveness of drugs manufacturers considered newly developed.¹⁰⁹

The FDA soon created the distinction between prescription and over the counter drugs.¹¹⁰ The FDCA required labeling to include both directions for use and warnings of possible harms from using the drug.¹¹¹ Exempt from this provision were the prescription drugs, those that the FDA believed could not

Session (Jan. 6, 1997).

¹⁰³ See Hayes, *supra* note 61, at 60.

¹⁰⁴ Pub. L. No. 57-244, 32 Stat. 728 (1902).

¹⁰⁵ Pub. L. No. 59-384, 34 Stat. 768 (1906).

¹⁰⁶ See Annette, L. Marthaler, *The FDA Defense: A Prescription for Easing the Pain of Punitive Awards in Medical Products Liability Cases*, 19 HAMLINE L. REV. 451, 462 (1996).

¹⁰⁷ See Hayes, *supra* note 61, at 60.

¹⁰⁸ See *id.*; Pub. L. No. 75-717, 52 Stat. 1040 (1938) (currently codified at 21 U.S.C. §§ 301 to 392).

¹⁰⁹ See Marthaler, *supra* note 105, at 463.

¹¹⁰ See Charles J. Walsh, Steven R. Rowland, & Howard L. Dorfman, *The Learned Intermediary Doctrine: The Correct Prescription for Drug Labeling*, 48 RUTGERS L. REV. 821, 825 (1996).

¹¹¹ See *id.*; Pub. L. No. 75-717, 52 Stat. 1040, 1050-51 (1938) (currently codified at 21 U.S.C. § 352(f)).

feasibly be labeled for patients to choose to use safely.¹¹² In addition, the FDA's enforcement powers grew as it developed administrative procedures to achieve compliance.¹¹³ In time, the concept of misbranding expanded to include failure to reveal "material facts."¹¹⁴ The 1951 Durham-Humphrey Amendments to the FDCA mandated that certain drugs needed to be prescribed by medical professionals. Prescription drug labels were required to contain "adequate information concerning [the drug's] safety and effectiveness for its intended use by the practitioner who dispenses."¹¹⁵ In addition, the label needed to provide directions for use and to fully disclose any warnings.¹¹⁶

The 1962, Kefauver-Harris amendments to the FDCA, significantly changed the way that the FDA regulated the labeling of drugs.¹¹⁷ The FDA began to base the approval of New Drug Applications (NDAs) on the labels submitted. Thus, all drugs had to be approved or generally recognized as safe based on substantial evidence that the drugs were both safe and effective.¹¹⁸ This gave the FDA a uniform requirement for labeling claims.¹¹⁹

On April 7, 1975, the FDA proposed a rule regarding the labeling for prescription drugs used in people.¹²⁰ The proposal was to improve prescription drug labels by requiring a specific format.¹²¹ The label would have sections, such

¹¹² See Walsh et al., *supra* note 109, at 825.

¹¹³ See Hayes, *supra* note 61, at 60.

¹¹⁴ *Id.*

¹¹⁵ *Id.* at 61.

¹¹⁶ See *id.*

¹¹⁷ See *id.*

¹¹⁸ See *id.*

¹¹⁹ See *id.* at 62; David G. Adams, *FDA Regulation of Communications on Pharmaceutical Products*, 24 SETON HALL L. REV. 1399, 1404 (1994).

¹²⁰ See Labeling for Prescription Drugs Used in Man; Proposed Format for Prescription-Drug Advertisements, 67 FED. REG. 15392 (1975).

¹²¹ See *id.*

as “Clinical Pharmacology,” “Indications and Usage,” “Adverse Reactions,” and “Precautions.”¹²² When the final rule was promulgated on June 26, 1979 the regulations required categories of information on the label and specified that labeling claims needed to come from testing on humans when feasible.¹²³

This 1979 regulation did address the issue of pediatric use in section 201.57(f)(9).¹²⁴ This regulation said that if there was a specific pediatric indication it should be described in the “Indications and Usage” section and then the appropriate pediatric dosage should be listed in the “Dosage and Administration” section of the labeling.¹²⁵ But, for pediatric use to appear on the label there needed to be “substantial evidence derived from adequate and well-controlled studies.”¹²⁶ Thus, most prescription drugs did not contain pediatric doses on the labels because the required clinical trials of children were not available.¹²⁷

The 1990 study by the American Academy of Pediatrics, which found that 80% of the drugs approved between 1984 and 1989 had no information on pediatric use, was the impetus for the October 16, 1992 FDA proposal to amend the “Pediatric Use” subsection of the Labeling regulations.¹²⁸ The FDA’s concerns were similar to the concerns about the lack of drug testing on children;

[w]ithout adequate information, physicians may be reluctant to pre-

¹²² See *id.* at 15393.

¹²³ See Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 FED. REG. 37434, 37434 (1979) (to be codified at 21 C.F.R. §§ 201-202); Hayes, *supra* note 61, at 62.

¹²⁴ 21 C.F.R. 201.57(f)(9) (1979).

¹²⁵ *Id.*

¹²⁶ *Id.*

¹²⁷ See Williams, *supra* note 18.

¹²⁸ See Specific Requirements on Content and Format of Labeling for “Pediatric Use” Subsection in the Labeling, 57 FED. REG. 47423, 47423 (1992).

scribe
certain drugs at all for their pediatric patients, or may prescribe them
inappropriately, choosing dosages, for instance that are arbitrarily
based
on the child's age, body weight, or body surface area without regard
for the interaction of those factors or age-related physiological and
biochemical factors. As a result, children may be exposed to an in-
creased
risk of adverse reactions, or decreased effectiveness of prescription
drugs,
or may be denied access to valuable therapeutic agents.¹²⁹

The FDA had finally recognized that due to the problems related to testing
drugs on children,¹³⁰ studies meeting the stringent standards in the 1979 reg-
ulation on pediatric use were difficult to obtain.¹³¹ Thus, the goal of the 1992
proposed regulation was to encourage pharmaceutical companies to increase the
labeling of drugs for pediatric use.¹³²

On December 13, 1994, a final regulation was promulgated revising the
“Pediatric Use” subsection of the prescription drug labeling requirements.¹³³ By
December 13, 1996, manufacturers were to submit supplemental labeling appli-
cations if substantial evidence of safety and effectiveness could be extrapolated
to children from adults.¹³⁴ In addition, if there was no substantial evidence of
pediatric use, the label was to indicate this fact.¹³⁵

Over time, the FDA has been able to increase its authority to regulate

¹²⁹ *Id.*

¹³⁰ See discussion *supra*, Part II(A).

¹³¹ See Specific Requirements on Content and Format of Labeling for “Pediatric Use” Sub-
section in the Labeling, 57 FED. REG. at 47423.

¹³² See *id.*

¹³³ See Specific Requirements on Content and Format of Labeling for Human Prescription
Drugs; Revision of Pediatric Use Subsection in the Labeling, 59 FED. REG. 64240 (1994)
(codified at 21 C.F.R. 201.57(f)(9)).

¹³⁴ See *id.*

¹³⁵ See *id.* See discussion *infra* Part IV(B).

the food and drug supply. This has finally enabled the FDA to promulgate a regulation that attempts to make drugs safer and more effective for children. Due to the limited amount of testing on children to determine appropriate pediatric dosages and the fact that pharmaceutical companies have extended the compliance date of this regulation,¹³⁶ it is clear that more needs to be done in this area.

IV. THE CURRENT STATUS REGARDING DRUG TESTING ON CHILDREN AND LABELING DRUGS FOR PEDIATRIC USE

“

Without pediatric studies or other sources of scientific information, labeling cannot include guidance about dosage, side effects, and when a drug should or should not be used in children.”¹³⁷ The most recent regulations are an attempt to encourage pharmaceutical companies to develop the pediatric information from clinical trials on children or extrapolation from adults so that this critical information can be included on the labels of medications.¹³⁸ As of today, these regulations have not succeeded in alleviating the need for data regarding pediatric use. This section will examine both the current regulations and the current conditions regarding both drug testing on children and labeling drugs for pediatric use.

¹³⁶ See *FDA Pediatric Use Supplement Submission Deadline Extended*, 59 F-D-C REP., (“The Pink Sheet”), Jan. 6, 1997, at T&G 6.

¹³⁷ Flieger, *supra* note 22.

¹³⁸ See *id.*

A. An Analysis of the Current Regulations for Protecting Children Involved as Subjects in Research

The final rule approved in 1983 essentially remains the same today.¹³⁹ Subpart D of the Protection of Human Subject Guidelines, entitled Additional Protections for Children Involved as Subjects in Research, enumerates important guidelines to protect the welfare of children.¹⁴⁰

1. Background Information: Sections 46.401 through 46.403

Section 46.401 establishes that Subpart D applies to all research conducted or supported by the Department of Health and Human Services that involves children as subjects.¹⁴¹ Section 46.402 defines important terms.¹⁴² Children are those who have not reached the legal age for consent to the research as per the laws of the applicable jurisdiction.¹⁴³ Assent is defined as a “child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.”¹⁴⁴ Permission is then the agreement by the child’s biological or adoptive parent(s) or guardian.¹⁴⁵ Section 46.403 expands the responsibilities of the Institutional Review Boards (IRBs) to include research involving children as subjects.¹⁴⁶

2. Determining Whether the Research Can and Should Be Done on Children; A Look at the Guidelines, IRBs, and the Requirements: Sections 46.404

¹³⁹See Additional Protection for Children Involved as Subjects in Research, 48 FED. REG. 9814 (1983) (codified at 45 C.F.R. §§ 46.401–46.409).

¹⁴⁰See *id.*

¹⁴¹See *id.* § 46.401.

¹⁴²See *id.* § 46.402.

¹⁴³See *id.* § 46.402(a).

¹⁴⁴*Id.* § 46.402(b).

¹⁴⁵See *id.* § 46.402(c)–(e).

¹⁴⁶See *id.* § 46.403.

through 46.407.

The next four sections address the level of risk to the child involved in research that the Department of Health and Human Services will conduct or fund.¹⁴⁷ Section 46.404 says that the Department of Health and Human Services will only conduct or fund research that the IRB finds has no greater than a minimal risk to children if there have been proper attempts to solicit assent from the children and permission from the parents.¹⁴⁸ Section 46.405 allows for research on children when there is a greater than minimal risk but the potential for direct benefit to the subjects¹⁴⁹ provided that the IRB finds “[t]he risk is justified by the anticipated benefits,”¹⁵⁰ “[t]he relation of the anticipated benefit to the risk is as least as favorable to the subjects as that presented by available alternative approaches,”¹⁵¹ and there have been the appropriate attempts to solicit both the assent of the child and the permission of the parent(s) or guardian(s).¹⁵² Section 45.406 is relevant to research that involves a greater than minimal risk and has no anticipated benefit to the individual child subjects, but is likely to “yield generalizeable knowledge about the subject’s disorder or condition.”¹⁵³ In this case, the Department of Health and Human Services will acquiesce with the project only if the IRB has found that

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or ex-

¹⁴⁷ See *id.* § 46.404-407

¹⁴⁸ See *id.* § 46.404.

¹⁴⁹ See *id.* § 46.405.

¹⁵⁰ *Id.* § 46.405(a).

¹⁵¹ *Id.* § 46.405(b).

¹⁵² See *id.* 46.405(c).

¹⁵³ *Id.* § 46.406.

pected
 medical, dental, psychological, social or educational situations;
 (c) The intervention or procedure is likely to yield generalizeable knowl-
 edge
 about the subjects' disorder or condition which is of vital importance
 for the understanding or amelioration of the subjects' disorder or con-
 dition; and
 (d) Adequate provisions are made for soliciting assent of the children
 and
 permission of their parents or guardians...¹⁵⁴

Lastly, Section 46.407 provides a catch-all for the Department of Health and Human Services to conduct or fund research not covered by the three sections outlined above.¹⁵⁵ As per this section, research is permissible if the Secretary (after consulting with a panel of experts from a variety of disciplines such as law, medicine and ethics) and the IRB find that “[t]he research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children”¹⁵⁶ and that the Secretary (after consultation) finds that the research “will be conducted in accordance with sound ethical principles,”¹⁵⁷ and that proper steps will be taken to get assent from the children and permission from the parent(s) or guardian(s).¹⁵⁸

These four sections, Sections 46.404 through 46.407, set guidelines for determining whether proposed research may be done on children.¹⁵⁹ Essentially then, Institutional Review Boards (IRBs) control the access children have to being part of clinical drug trials.¹⁶⁰ This is especially true because even

¹⁵⁴ *Id.*

¹⁵⁵ *Id.* § 46.407.

¹⁵⁶ *Id.* § 46.407(a); §46.407(b)(i).

¹⁵⁷ *Id.* § 46.407(b)(ii).

¹⁵⁸ *Id.* § 46.407(b)(iii).

¹⁵⁹ *See id.* § 46.404-407.

¹⁶⁰ *See* Dale L. Moore, *An IRB Member's Perspective on Access to Innovative Therapy*, 57 ALB. L. REV. 559, 559 (1994).

though the aforementioned federal guidelines for IRBs only refer to research funded or conducted by the Department of Health and Human Services, many IRBs do not evaluate federally-sponsored and privately-sponsored research proposals differently.¹⁶¹ One IRB member, Dale Moore, who has written on this issue said, “[w]e must be particularly vigilant about protecting vulnerable populations, including children, prisoners, pregnant women, the mentally disabled, and those who are economically or educationally disadvantaged. The vulnerability of people in these groups stems from their susceptibility to exploitation or coercion.”¹⁶² While there are concerns about protecting “vulnerable” people, Moore acknowledged that child welfare mandates the use of children in drug testing.¹⁶³ Thus, in his opinion, the key is to make sure that IRBs act as “advocates for the research subjects.”¹⁶⁴

The regulations and the IRBs are not the major problem when it comes to ensuring research involving children is not disadvantageous. The FDA has come to see the importance of testing drugs on children. For example, the FDA has recently added a “pediatric page” to its review of NDAs so that there is a summary of what is known about the drug with respect to children.¹⁶⁵ The greater difficulty is getting institutions to test the drugs in the first place, leaving most drugs with disclaimers saying that safety and effectiveness have not been established for use in children.¹⁶⁶ For economic reasons, institutions tend

¹⁶¹ *See id.* at 564.

¹⁶² *Id.* at 565.

¹⁶³ *See id.* at 570.

¹⁶⁴ *Id.* at 572.

¹⁶⁵ *See Drug Testing in Children*, *supra* note 5.

¹⁶⁶ *See id.*

not to perform clinical trials on children.¹⁶⁷ Thus, for children to have access to the drugs they need in appropriate dosages, more clinical testing is needed.

The National Institute of Child Health and Human Development (NICHD) has now established a network of six research sites that are providing clinical data on drug use in children.¹⁶⁸ Dr. Duane Alexander, director of NICHD says that the goal of this program is to increase the number of drugs tested on children and then ultimately approved by the FDA for use in children so that eventually, “all drugs prescribed for children [will] have been evaluated and approved specifically for such usage.”¹⁶⁹

In 1994, the American Academy of Pediatrics’ Committee on Drugs gave the FDA a list of six drugs that most crucially needed to be approved for children. These drugs include three anesthetics: midazolam (Versed), bupivacaine (Sensorcaine), and fentanyl which are all used in emergency settings for surgery, bone-setting, or diagnostic procedures such as CAT-scans.¹⁷⁰ The other three drugs were Flagyl (an antibiotic), Tagament (an ulcer medication) and albuterol (an asthma medication).¹⁷¹

3. *Child’s Assent and Parent(s)’ Permission: Section 46.408*

The regulations for using children as research subjects also address the issues of assent and permission for participation in Section 46.408.¹⁷² Here it says that the IRB must determine whether a child is capable of assenting and if

¹⁶⁷ See *id.*; Wielawski, *supra* note 13, at E1. See also Kessler, *supra* note 1 at 330.

¹⁶⁸ See Ostrowidski, *supra* note 2, at 1.

¹⁶⁹ *Id.*

¹⁷⁰ See Elizabeth Stone, *Children’s Labels Reconsidered*, N.Y. TIMES, Jan. 25, 1995, at C11.

¹⁷¹ See *id.*

¹⁷² 45 C.F.R. § 46.408 (1996).

so, whether the assent has been adequately solicited.¹⁷³ In making this decision the IRB will take into account age, maturity, and psychological state for each child individually or for all children to be involved in the study.¹⁷⁴ If the IRB finds that the child is not capable of assenting, the assent requirement can be waived.¹⁷⁵

The IRB must also determine whether parent(s)' permission was adequately sought.¹⁷⁶ If the research has no greater than a minimal risk to the child (§46.404) or the research has a greater than minimal level of risk, but would be of direct benefit to the child participating (§46.405), the permission of one parent is needed. If, however, the research is not meant to directly benefit the child (§§ 46.406 and 46.407), the permission of both parents is required unless one is deceased, unknown, incompetent, not reasonably available, or if only one parent has legal responsibility for the child.¹⁷⁷ The IRB can determine that the research does not need parental permission so long as there is another mechanism to protect the child participants and this is consonant with state and federal law.¹⁷⁸

A child's assent (or lack thereof) is of great value in determining whether the research should be done. Some children, however, are powerless when it comes to these choices, especially younger children.¹⁷⁹ In general, children are opposed to medical care. Crying, screaming, and tantrums are common

¹⁷³ See *id.* § 46.408(a).

¹⁷⁴ See *id.*

¹⁷⁵ See *id.*

¹⁷⁶ See *id.* § 46.408(b).

¹⁷⁷ See *id.*

¹⁷⁸ See *id.* § 46.408(c).

¹⁷⁹ See Moore, *supra* note 160, at 569.

occurrences for children at the doctor's office. A child's resistance to medical treatment may sometimes be ignored, which could be in the child's best interest.¹⁸⁰

There are instances where a parent's lack of permission can be overridden by a child's assent. Some states have lowered the age at which minors can consent to medical treatment.¹⁸¹ The law has been increasingly recognizing that age is arbitrary and that therefore, some decisions should be based on maturity.¹⁸² The federal regulations recognize that there are some children that should make their own choices regarding their participation in research studies.¹⁸³

4. *Children Who are Wards of the State: Section 46.409*

Section 46.409 allows children who are wards of the state to be included in research if the research is related to their status as wards, or if the research is conducted in settings such as schools, camps, and, hospitals, or institutions where most children are not wards of the state.¹⁸⁴ If the ward of the state is involved as a subject in research as described above, the IRB will appoint an advocate for each ward, who will act in the child's best interest.¹⁸⁵ Thus, for a child in foster care to be involved in a clinical trial, the research must either pertain to the child's status as a ward of the state or the research must involve

¹⁸⁰ See *id.* at 574.

¹⁸¹ See Glantz, *supra* note 21, at 112. See, e.g., *Younts v. St. Francis Hospital*, 469 P.2d 330 (Kan. 1970) (holding that a seventeen year old minor was mature enough to consent to a beneficial skin graft treatment); *In re E.G., a minor*, 549 N.E.2d 322 (Ill. 1989) (holding that a seventeen year old Jehovah's Witness with leukemia could refuse blood transfusions).

¹⁸² See *id.* at 113.

¹⁸³ See *id.*; 45 C.F.R. § 46.408.

¹⁸⁴ See 45 C.F.R. § 46.409(a).

¹⁸⁵ See *id.* at 46.409(b).

both children who are wards and children who are not as well as take place in a school, camp or hospital.¹⁸⁶ Most likely, these regulations are an attempt to protect foster children from the exploitation wards had experienced in earlier times, by prohibiting the exclusive use of wards of the state in pediatric research, while recognizing the need for these children to participate as subjects.¹⁸⁷

AIDS drug testing is an example showing that the reality of the situation is a bit more bleak. While wards of the state were clearly taken advantage of in earlier times,¹⁸⁸ these children now do not have enough access to participation in clinical trials.¹⁸⁹

In 1994 there were approximately one million children worldwide infected with the HIV virus and by the year 2000 there will be about ten million children suffering.¹⁹⁰ In the United States there are currently about 10-20,000 children with HIV.¹⁹¹ HIV infected foster children make up almost half of these children,¹⁹² yet a 1989 nationwide study found that only two percent of the children participating in AIDS related clinical trials were in foster care.¹⁹³

When foster children enter the system, they often lose contact with their biological parents, yet remain in “foster care drift” for an average of 5.7 years.¹⁹⁴ The result is that the children are unable to obtain parental consent to

¹⁸⁶ See *id.* at 46.409(a).

¹⁸⁷ See Briar McNutt, *The Under-Enrollment of HIV-Infected Foster Children in Clinical Trials and Protocols and the Need for Corrective State Action*, 20 AM. J. L. AND MED. 231, 241 (1994).

¹⁸⁸ See discussion *infra* Part III(A).

¹⁸⁹ See McNutt, *supra* note 187, at 231.

¹⁹⁰ See *id.*

¹⁹¹ See *id.*

¹⁹² See *id.* at 237.

¹⁹³ See *id.* at 231.

¹⁹⁴ The average length of time from when a child first enters foster care in Massachusetts until the child’s adoption is legalized is 5.7 years. Report by the Probate and Family Court, Honorable Mary C. Fitzpatrick, Chief Justice, *Termination of Parental Rights Cases in the*

participate in the drug testing.¹⁹⁵ While the federal regulations on children as research subjects would not prohibit participation, most child protection agencies do not have the authority to consent to treatment with investigational or experimental drugs.¹⁹⁶ Therefore, at this time there is a large segment of the HIV population unable to obtain access to new drug therapies.

B. An Analysis of the Current Regulation of Labeling Drugs for Pediatric Use

The FDA is in the midst of revolutionizing drug labeling so that medical professionals will be cognizant of appropriate pediatric doses and safety hazards. On December 13, 1994, the FDA promulgated a final rule revising the “Pediatric Use” subsection of labeling drugs.¹⁹⁷ The purpose of this new regulation was to change the 1979 regulation which only permitted pediatric claims if there had been adequate and well-controlled studies of the drug on children.¹⁹⁸ This old regulation had, contrary to its purpose, stymied the hope that drug labels would provide adequate information for using drugs in children.¹⁹⁹ The new regulation offers much more promise that drugs will be labeled with more pediatric information, information that is critical to the well-being of so many of our nation’s youngest.

The new regulation, effective January 12, 1995, revamped drug la-

Probate and Family Court: Recommendations for Improvements to the System (March 1, 1995).

¹⁹⁵ See McNutt, *supra* note 187, at 242.

¹⁹⁶ See *id.*

¹⁹⁷ See Specific Requirements on Content and Format of Labeling for Human Drugs; Revision of “Pediatric Use” Subsection In the Labeling, 59 FED. REG. 64240 (1994) (codified at 21 C.F.R. § 201.57(f)).

¹⁹⁸ See *id.*

¹⁹⁹ See *id.*

belong for pediatric use.²⁰⁰ The regulation upheld the earlier requirement so that if there was a specific pediatric indication supported by adequate and well-controlled studies in the pediatric population, this would appear on the label.²⁰¹ In addition, the FDA could now approve a drug for pediatric use based on adequate and well-controlled studies in *adults* if other information supporting pediatric use was provided and the FDA determined that the course of the disease and the effects of the drug were similar in adults and children.²⁰² Also, if there was not substantial evidence to support a pediatric indication or a pediatric use statement for any children, (or for a specific age group), the “Pediatric Use” subsection of the label will need to say that “safety and effectiveness in pediatric patients [or the age group] have not been established.”²⁰³

Sponsors of drugs were given until December 13, 1996, two years after the final regulation was promulgated, to look at their data and determine whether the “Pediatric Use” subsection should be updated to include information supporting pediatric use based on studies in adults, and then submit a supplemental application to the FDA.²⁰⁴ Thus, if there is adequate data to support pediatric use, sponsors should seek supplemental claims; if there is not substantial evidence to support pediatric use then the label should state this; and if there is no reason for a “Pediatric Use” subsection on the label, the sponsor should justify its omission to the FDA.²⁰⁵ In essence, as FDA Commissioner,

²⁰⁰ See *id.*

²⁰¹ See 21 C.F.R. 201.57(f)(9)(ii)-(iii) (1996).

²⁰² See *id.* at 201.57(f)(9)(iv).

²⁰³ *Id.* at 201.57(f)(9)(v)-(vi).

²⁰⁴ See *Pediatric Use Drug Labeling NDA Supplements Due By December 1996—FDA Final Rule*, 56 F-D-C REP. (“The Pink Sheet”), Dec. 19, 1994, at 3.

²⁰⁵ See *id.* at 4.

David Kessler, said when the final rule was announced at the Food and Drug Law Institute annual meeting,

“[t]he new rule also allows the FDA to approve a drug for pediatric use when the course of a disease is similar in adults and children, and the sponsor provides supporting pediatric information.... So, if the disease behaves the same in adults and children, adequate and well-controlled trials to show efficacy may not need to be repeated in children. All that may be necessary under the new rule is information on the appropriate dose for children and perhaps some additional safety information.”²⁰⁶

On November 6, 1996, after very little response to the final rule, the FDA sent letters to 250 drug manufacturers asking them to tell the agency if they planned to file supplements, and if so when.²⁰⁷ As of December 30, 1996, only 40 of the pharmaceutical companies had responded to the FDA’s letter.²⁰⁸ On November 20, 1996, the Pharmaceutical Research and Manufacturers of America (PhRMA) asked the FDA to extend the compliance date because some of its members with a lot of different products, were having trouble gathering the necessary information.²⁰⁹

The FDA, knowing compliance is essential to the success of their new pediatric use labeling requirement, decided to extend the compliance date of the final rule to April 7, 1997.²¹⁰ Those manufacturers who let the FDA know

²⁰⁶ See Kessler, *supra* note 1, at 330.

²⁰⁷ See *FDA Pediatric Use Supplement Submission Deadline Extended*, 59 F-D-C REP. (“The Pink Sheet”), Jan. 7, 1997, at T&G-6; Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling; Extension of Compliance Date, 61 FED. REG. 68623 (1996).

²⁰⁸ See *id.*

²⁰⁹ See *id.*

²¹⁰ See *id.*

in writing by January 29, 1997 that they intend to submit supplemental applications for their products, will have until April 7, 1997 to gather the required data.²¹¹ As of this date, it remains to be seen just how much compliance there will be; therefore, it is not clear how successful this new regulation will be.

“The absence of adequate pediatric labeling continues to present a significant public health issue and the level of response to the December 13, 1994, final rules is cause for concern,” read the Federal Register when the FDA decided to extend the compliance date.²¹² The nature of the problem is that the information regarding pediatric use is just not available with regard to many, many drugs commonly used in children. Doctors had been “guesstimating” doses. Now manufacturers asked for information regarding the pediatric use of drugs cannot find the adequate data. Why? Because the data does not exist. And the reason for this is that the pharmaceutical companies do not want to pay for the research because the market for children’s drugs is not sufficient to compensate for the costs of the studies. Thus, it is quite possible that even with this new regulation, making it substantially easier to label drugs for pediatric use, the crucial information will still not be available to medical professionals.

V. MAKING DRUGS MORE SAFE AND EFFECTIVE FOR USE IN CHILDREN: SOME RECOMMENDATIONS FOR INCREASING DRUG TESTING ON CHILDREN AND LABELING DRUGS FOR PEDIATRIC

²¹¹ See *id.*

²¹² Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling; Extension of Compliance Date, 61 FED. REG. 68623, 68623 (1996).

USE

FDA Commissioner, David Kessler, referred to the new pediatric labeling regulation as “only a first step.”²¹³ Hopefully the new FDA Commissioner will agree with that statement because there is a lot more that needs to be done to ensure that our children can use safe and effective drugs in the appropriate doses. An analysis of this issue reveals several recommendations for combating the lack of information available regarding the pediatric use of drugs.

A. Increase the Length of Exclusivity for Manufacturers Who Have Their Drugs Approved for Pediatric Use

If a major obstacle to testing drugs on children is that it is not economically feasible for drug manufacturers to do the studies, then providing financial incentives for drug testing on children could eventually lead to enough data for most drugs to be labeled for pediatric use. One way to provide financial incentives for manufacturers to test their drugs on children is to treat this problem similarly to the testing of “orphan drugs” by providing increased market exclusivity.

Orphan drugs are those that are necessary to treat “rare disease[s] or condition[s],” meaning diseases or conditions afflicting less than 200,000 people in the United States or afflicting more than 200,000 people but with no reasonable expectation that the cost of developing and making the drug can be

²¹³Kessler, *supra* note 1, at 330.

recovered through sales.²¹⁴ These drugs are given market exclusivity for seven years²¹⁵ which prevents other companies from piggybacking on their expensive research for a longer period of time than just when the patent would dictate. In addition, sponsors of such drugs can obtain open protocols for investigations on those with the disease or the condition.²¹⁶ Lastly, the Secretary of the Department of Health and Human Services can contract with or give grants to the drug sponsor in an effort to defray the costs of testing orphan drugs.²¹⁷

In 1992, as the FDA was proposing the regulation to change pediatric use labeling, Senator Nancy Kassebaum sponsored the “Better Pharmaceuticals for Children Act,” as an attempt to expand the orphan drug concept to testing drugs on children.²¹⁸ On October 5, 1992, Senator Kassebaum’s statements were read to Congress. She explained that, [w]ith the exception of certain drugs with known and significant pediatric uses, pharmaceutical product are seldom studied in younger populations,”²¹⁹ leaving the physicians to estimate safe and effective dosages for children even though children metabolize drugs differently from adults.²²⁰ The Senator claimed that the reason for this lack of information was that manufacturers had little incentive to do studies on drugs which they were not intending to market for children; those that they expected little addi-

²¹⁴Federal Food, Drugs, and Cosmetics Act, 21 U.S.C. § 360bb (1996).

²¹⁵*See id.* § 360cc.

²¹⁶*See id.* § 360dd.

²¹⁷*See id.* § 360ee.

²¹⁸*See* S. 3337, 102nd Cong. (1992); 54 F-D-C- REP. (“The Pink Sheet”), October 19, 1992, at 5.

²¹⁹*Statements on Introduced Bills and Joint Resolutions, Better Pharmaceuticals for Children Act*, S. 3337, 102nd Cong., 138 CONG. REC. S16998, S16998 (1992) [hereinafter *Statements*] (statements of Senator Nancy Kassebaum).

²²⁰*See id.*

tional revenue to come from the pediatric population.²²¹ This, she said, leaves children as “therapeutic orphans.”²²²

The Kassebaum bill would have provided incentives for manufacturers to test drugs on children. Essentially, any drug not ordinarily studied in children (so, not antibiotics, anti-asthmatic medications, anti-allergy medications, or drugs developed for diseases or conditions only occurring in children), would qualify for an additional six months of exclusivity provided that the FDA had approved the pediatric studies.²²³

Incentives are clearly needed for manufacturers to test their drugs on children. Eighty percent of the more than 2000 prescription drugs approved by the FDA have not been tested for safety or effectiveness in children.²²⁴ Only three of the nine AIDS drugs being sold have been approved for children.²²⁵ The major reason for this travesty seems to be a lack of economic incentives for drug manufacturers to invest in such research. Thus, if conducting these trials could be made profitable for manufacturers, the benefits to children could be enormous. The concept of extending exclusivity is not a new one; it has been successful in the realm of orphan drugs²²⁶ and could probably be as successful for pediatric use of drugs. Unfortunately, the Better Pharmaceuticals for Children Act did not get much past the Senate Floor of the 102nd Congress. Similar legislation needs to be introduced again, with a sponsor who will push the issue

²²¹ See *id.* at S16999; 54 F-D-C REP. (“The Pink Sheet”), October 19, 1992, at 5.

²²² *Statements*, *supra* note 217, at S16999.

²²³ See *id.*; S. 3337; 54 F-D-C REP. (“The Pink Sheet”), October 19, 1992, at 5.

²²⁴ See Stone, *supra* note 31, at A1.

²²⁵ See Gordon, *supra* note 27, at A1.

²²⁶ See *Hearings*, *supra* note 217, at S16998.

so that drug testing on children will be a reality that will ultimately end with pediatric use on drug labels. As Senator Kassebaum stated, “I know each of us would do anything to help a sick child, and an incentive for drug sponsors to perform pediatric studies takes a step in that direction.”²²⁷

B. Mandate Testing of Some Drugs and/or Mandate Label Supplements Indicating Pediatric Use

The fact that eighty percent of the approved drugs have not been tested for safety or effectiveness in children²²⁸ obviously cannot be remedied over night. We are quite far from the FDA goal that “whenever a child receives medication, it is as safe and effective as possible.”²²⁹ One way to manageably resolve this problem, would be for the FDA (or a child-oriented, health organization) to prioritize which drugs should be dealt with immediately and then work from there to eventually have them all approved for pediatric use either through testing on children or when feasible, extrapolating from adults. Perhaps Congress could provide some of the funds for the testing.

Some steps have been taken in this direction. In 1994, in response to an FDA request, the American Academy of Pediatrics submitted a list of the six drugs believed to most desperately need testing in children.²³⁰ These identified drugs were targeted because of their frequent use, potential safety hazards, and their therapeutic importance to children.²³¹ An IND for an oral syrup ver-

²²⁷See *id.* at S16999.

²²⁸See *Rule Would Help Doctors*, *supra* note 10, at 6.

²²⁹Williams, *supra* note 18.

²³⁰See Stone, *supra* note 31, at A1.

²³¹See *FDA Seeking Advisory Committee Input to Identify Drugs for Pediatric Indications*, 58 F-D-C REP. (“The Pink Sheet”), Dec. 23, 1996, at 18.

sion of the anesthesia, Versed, one of the six drugs identified by the American Academy of Pediatrics, was filed in December of 1996.²³² The FDA hopes to approve this application in 1998.²³³ In January of 1997, Paula Botstein, now the Acting Director of the FDA's Office of Drug Evaluation III, explained that one of the "next steps" in updating pediatric labeling is that the FDA is considering advisory committees which would identify the drugs that need pediatric indications.²³⁴ Botstein then explained the agency's efforts in this area by discussing the FDA's success in obtaining a pediatric use supplement for Versed.²³⁵

This effort does not seem sufficient. Of the almost 1600 drugs not yet approved for children,²³⁶ the American Academy of Pediatrics selected six critical drugs to be tested for pediatric use. Two years after the improved labeling regulation, only one of these six drugs has a pediatric supplement and the IND will not be approved until 1998.

A very strong effort to encourage manufacturers to submit supplemental applications for pediatric labeling, by the April 7, 1997 compliance date could reduce the number of drugs still lacking pediatric use information. From there, the FDA will need to intensively pursue the task of collecting data for those drugs that are used most frequently by children, possess the greatest potential of safety hazards, and have the greatest therapeutic importance for children.

Grant money from Congress could help this process move more swiftly.

²³²See *Roche Versed Pediatric Labeling Should Require "Dedicated Monitor" in Deep Sedation Cases, FDA Committee Says; Firm Submits IND for Oral Syrup Version*, 58 F-D-C REP. ("The Pink Sheet"), Dec. 23, 1996, at 17.

²³³See *id.*

²³⁴See *FDA Pediatric Use Supplement Submission Deadline Extended*, 59 F-D-C REP. ("The Pink Sheet"), Jan. 6, 1997, at T&G-6.

²³⁵See *id.*

²³⁶See *Rule Would Help Doctors*, *supra* note 10, at 6.

C. Create a Database of Information Relevant to Pediatric Use of Drugs

One major impediment for pharmaceutical companies attempting to comply with the new pediatric use labeling regulation is that often, they really do not have the data relevant to pediatric use. Health professionals who work with children can be a great source of information because many have already been prescribing these drugs for their pediatric patients. If the FDA could create a database, physicians from all over the country could share the experiences they have had using the drugs lacking data from clinical trials. In essence, since pediatricians are currently relying on trial and error to estimate doses, it is as if there are clinical trials being run throughout the country. If this was all entered into one database, the FDA could come up with the proper dosages to make drugs safe and effective for children.

Currently, there is a Pediatric Oncology Group which is a successful data bank relevant to the use of cancer drugs in children.²³⁷ It would be extremely helpful for children if this concept could be expanded. Eventually, the FDA could approve drugs for pediatric use and then label the drugs for pediatric use, without requiring the manufacturers to sponsor expensive studies.

This system has some potential flaws. First of all, it would take additional FDA resources to create a database. Secondly, compiling this information could take a great deal of time. On the other hand, the current system is also going to take a tremendous amount of time, if it ever works. Physician compliance is another potential problem, but it seems like it would be easier to enlist the

²³⁷See Wielawski, *supra* note 13, at E1.

services of physicians than the pharmaceutical companies. Lastly, if the FDA started to take responsibility for assessing pediatric use, manufacturers would probably not test their new drugs on children. It would, therefore, be best if the FDA database was only used to approve drugs that have already been on the market and used on children and for experimental drugs. New drugs, however, probably should not be included in the database. Instead, manufacturers should be encouraged to test their drugs on children prior to having the drug approved by the FDA.

D. Encourage Pediatric Testing During the Development of New Drugs

If more manufacturers had data regarding the pediatric use of drugs during the development process, it would be much easier to label the drugs for pediatric use once they were put on the market.

According to Paula Botstein, in 1995 the FDA was already routinely asking FDA drug review divisions to find the INDs with potential pediatric uses and then encourage the drug companies to go through the process of having these drugs approved for children.²³⁸ Ms. Botstein also said that the FDA has created a “pediatric page,” which is a summary of what is known about a drug with respect to children used during NDA review.²³⁹ “It’s basically a management tool, so that FDA’s own people will think more in terms of drugs for children— and to explore this potential with the drug sponsors.”²⁴⁰

The problem here is that the FDA cannot do more than encourage drug manufacturers to study their drugs in children. Neither labeling drugs for

²³⁸ See

²³⁹ See *id.*

²⁴⁰ See *id.*

pediatric use nor testing drugs in children are requirements for the approval of NDAs. Amending the Federal Food, Drug, and Cosmetics Act to require drug testing on children prior to drug approval, would probably slow down the approval process, keeping vital drugs off of the market.

Drug companies need to value children when they make their choices. Perhaps if the FDA continues to encourage drug companies to investigate drug effects on children, the mindset of manufacturers will shift. In addition, if the FDA “encourages” drug companies through more expeditious and cooperative review of NDAs containing information regarding pediatric use, manufacturers might be urged to incorporate children’s needs into their corporate decisions. The key again is financial incentives for drug manufacturers.

Perhaps, if there were these incentives for testing new drugs on children, Congress could then provide some of the funds and create a data base for pediatric use of drugs already on the market. In addition, the new labeling regulation makes the approval process easier because drugs need not actually be tested in children provided there is substantial evidence that the data can be extrapolated from adults and that the course of the disease and the drug are similar in both children and adults. Putting these concepts together, it is possible that eventually there would be enough data on the safety and effectiveness of drugs in children that most drugs could be labeled for pediatric use.

E. Strengthen the Institutional Review Boards (IRBs)

The thought of drug testing children still makes the public cringe. No one thinks that children should be used as guinea pigs. Ethics is a real concern

when it comes to drug testing and children. Public support of using children in clinical trials is necessary if the proper resources are going to be available for this mission. One way to increase public support would be to increase the credibility of IRBs in the eyes of the public.

IRBs essentially determine whether research will be done using children as subjects.²⁴¹ Trust in this choice that could mean the difference between the life and the death of a child is imperative.

IRBs need to scrupulously analyze research applications when deciding whether or not the research is permissible. This is especially true with vulnerable populations, such as children. If IRBs are seen as adept, many of the ethical concerns will be eliminated. More drug testing on children would be funded both publicly and privately, if the public viewed this testing as both critical and ethical. In addition, drug manufacturers would no longer be able to claim that ethical concerns were the basis for their lack of testing; drug manufacturers would have to face up to their choice not to do drug testing on children because it is not cost-effective.²⁴²

CONCLUSION

Our society run by grown-ups has failed to protect the health and safety of our children. Inevitably, children will need medications, but the chances are

²⁴¹ See Moore, *supra* note 160, at 559.

²⁴² See Wielawski, *supra* note 13, at E1.

that the drugs prescribed will not have been approved for use in children. This is unacceptable.

The problem is clear. Children metabolize and excrete drugs differently than adults. Therefore, determining dosages and safety hazards for children typically requires testing in children. Since these tests are rarely done, most drug labels tell pediatricians nothing about pediatric use.

We are at a critical time in history, a time when child welfare is on political agendas. Thus, it is time to make some changes so that children will have access to vital drugs in appropriate dosages.

The Food and Drug Administration finally sees the urgency for drug testing on children and labeling drugs for pediatric use. Now political leaders have the responsibility to make sure that the pharmaceutical companies respond. We cannot leave the issue of drug testing on children to the market because it is not profitable for drug manufacturers to do the needed studies. A child's life, however, is priceless. Steps need to be taken to make sure that when children are given medication, the dosage is as accurate as possible. This is what adults want and this is what adults generally get. Children deserve at least this much.